

1088.550



PATENT SPECIFICATION

NO DRAWINGS

1088.550

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COMPLETE SPECIFICATION

N-substituted 3-imino-benzisothiazolines and their production

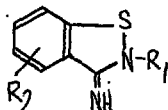
We, FARBENFABRIKEN BAYER AKTIENGESellschaft, a body corporate organised under the laws of Germany, of Leverkusen-Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new antimycotic agents of reduced toxicity and improved skin compatibility and more particularly to new N-substituted 3-imino-benzisothiazolines and their preparation.

The available literature on the antimycotic activity of benzisothiazolones - 3 [Survey in Arzneimittelforschung 14, 1301 (1964)] is known to be extensive.

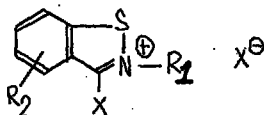
However, N - substituted 3 - imino - benzisothiazolines are new compounds and antimycotic agents have not hitherto been described in the literature.

It has now been found that these new compounds of the formula:



I

are obtained when N-substituted 3-halogeno-benzisothiazolium halides of the formula:



II

are reacted with ammonia.

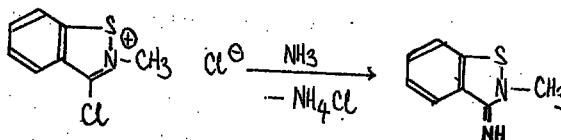
In the above formulae I and II, X is a halogen atom, especially Cl or Br, R₁ is an alkyl of 1 to 7 carbon atoms, a cycloalkyl, an arylalkyl or an aryl radical which may be substituted by halogen, nitro, alkyl or alkoxy containing 1 to 6 carbon atoms or dialkylamino containing 2 to 12 carbon atoms and R₂ is one or more of the following: hydrogen, halogen, nitro, alkyl and alkoxy containing 1 to 6 carbon atoms.

The new N - substituted 3 - imino - benzisothiazolines are excellent antimycotic agents. Their activity can be regarded as at least as good as that of the known benzisothiazolones - 3, and even superior in some instances. Compared with the known benzisothiazolones-3, they are appreciably less toxic and unlike other agents they exhibit an excellent skin compatibility.

When N - methyl - 3 - chloro - benzisothiazolium chloride is employed as the

[Price 4s. 6d.]

starting material, the reaction sequence may be represented by the following scheme of formulae:



In carrying out the process according to the invention, 1 mole of the N-substituted 3 - halogeno - benzisothiazolium halide is preferably introduced at 5° to 10°C. into an excess of ammonia, preferably into a solution of NH_3 in methanol (1 litre 5 M NH_3).

The N - substituted 3 - halogeno - benzisothiazolium halides employed as the starting material, preferably N - substituted 3 - chloro - benzisothiazolium chlorides, may be prepared from N-substituted dithiosalicylic acid amides and phosphorus pentahalides.

The N - substituted 3 - imino - benzisothiazolines are colorless crystalline compounds. They are weak bases and as a consequence they only form salts with strong acids.

In vitro, they exhibit excellent inhibition values for *Trichophyton mentagrophytes*, *Candida albicans*, *Penicillium commune*, *Aspergillus niger* and *Microsporium felineum*. Some of the compounds also exhibit a distinct activity towards the experimental guinea pig trichophytis on peroral administration.

The new compounds are intended to serve as antimycotic agents in human and veterinary medicine, and also as plant protection agents.

The invention is illustrated by the following non-limitative Example:

EXAMPLE

N - methyl - 3 - imino - benzisothiazoline . HCl
110 g (0.5 mole) of N - methyl - 3 - chloro - benzisothiazolium chloride (finely powdered) are introduced portionwise at 5° to 10° C. into 500 ml of a saturated solution of NH_3 in methanol (2.5 moles) while stirring vigorously. Stirring is continued for another 5 minutes in order to complete the reaction, the precipitated ammonium chloride is then filtered off with suction, and the filtrate is evaporated *in vacuo*. The resultant syrup is taken up in 150 ml of 1:1 hydrochloric acid (0.75 mole). The initially clear solution solidifies to a solid pulp after a few minutes. After standing in an ice bath for some time (30 minutes), the hydrochloride which has crystallized out is filtered off with suction, washed with a little cold water and dried. 55 G (55% of the quantitative yield) of N - methyl - 3 - imino - benzisothiazoline . HCl are obtained. The compound crystallizes from ethanol as colorless prisms of melting point 220° C(sublim).

The compounds specified below are prepared by the same method:

N - ethyl - 3 - imino - benzisothiazoline.HCl

After recrystallization from ethanol, this substance produces colorless, well defined leafy prisms of m.p. 171°C. (sublim.).

N - propyl - 3 - imino - benzisothiazoline.HCl

Colorless prisms of m.p. 111° C., from methanol.

N - butyl - 3 - imino - benzisothiazoline.HCl

This compound crystallized from acetonitrile in the form of colorless compact prisms which melt at 155° to 157° C., then crystallize again and exhibit a second m.p. at 212° C.

N - isobutyl - 3 - imino - benzisothiazoline.HCl

On recrystallization from methanol this substance is obtained in the form of large colorless plates which melt at 187° C., then crystallize again and exhibit a second m.p. at 216° C.

N - [β - chloroethyl] - 3 - imino - benzisothiazoline.HCl

Colorless, compact, well defined prisms of m.p. 152° C. (from methanol).

N - cyclohexyl - 3 - imino - benzisothiazoline.HCl
Colorless compact prisms of m.p. 166° C.

N - [4 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl
After recrystallization from ethoxyethanol, colorless crystals of m.p. 160° C.

5 N - [3 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl
Colorless small needles of m.p. 197° C., from ethanol.

N - [2 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl
On recrystallization from DMSO, the compound produces colorless prisms of m.p. 210° C.

10 N - benzyl - 3 - imino - benzisothiazoline.HCl
This substance was isolated in the form of the free base. The compound forms colorless compact prisms of m.p. 85° C. (from methanol).

N - phenyl - 3 - imino - benzisothiazoline
This compound was isolated in the form of the free base. Colorless bulbous crystals of m.p. 99°C. (from ethanol).

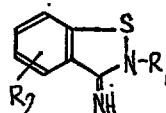
N - [4 - methyl - phenyl] - 3 - imino - benzisothiazoline
The free base crystallizes from ethanol in the form of long yellowish needles of m.p. 144°C.

20 The invention therefore also provides an antimycotic composition comprising a compound according to the invention in admixture with a solid or liquid diluent or carrier. The selection of a particular diluent or carrier and the exact proportions used may of course be in accordance with general practice.

25 The invention therefore also provides a method of combating mycotic pests, comprising apply to a mycotic pest habitat a compound according to the invention, alone or in admixture with a solid or liquid diluent or carrier.

WHAT WE CLAIM IS:—

1. An N - substituted 3 - imino - benzisothiazoline of the formula:—



in which

30 R₁ is an alkyl of 1 to 7 carbon atoms, a cycloalkyl, an aralkyl or an aryl radical, which may be substituted by halogen, nitro, alkyl or alkoxy containing 1 to 6 carbon atoms or dialkylamino containing 2 to 12 carbon atoms, and

R₂ is at least one of hydrogen, halogen, nitro, alkyl and alkoxy containing 1 to 6 carbon atoms and strong acid salts thereof.

35 2. N - methyl - 3 - imino - benzisothiazoline.HCl.

3. N - ethyl - 3 - imino - benzisothiazoline .HCl.

4. N - propyl - 3 - imino - benzisothiazoline .HCl.

5. N - butyl - 3 - imino - benzisothiazoline.HCl.

6. N - isobutyl - 3 - imino - benzisothiazoline .HCl.

40 7. N - [β - chloroethyl] - 3 - imino - benzisothiazoline.HCl.

8. N - cyclohexyl - 3 - imino - benzisothiazoline .HCl.

9. N - [4 - methylcyclohexyl] - 3 - imino - benzisothiazoline.HCl.

10. N - [3 - methylcyclohexyl] - 3 - imino - benzisothiazoline .HCl.

11. N - [2 - methylcyclohexyl] - 3 - imino - benzisothiazoline .HCl.

45 12. N - benzyl - 3 - imino - benzisothiazoline .HCl.

13. N - phenyl - 3 - imino - benzisothiazoline.

14. N - [4 - methyl - phenyl] - 3 - imino - benzisothiazoline.

15. A process for the preparation of a compound of claim 1 which comprises reacting an N - substituted 3 - halogeno - benzisothiazolium halide with ammonia.

50 16. A process for the preparation of a compound of claim 1 which comprises re-

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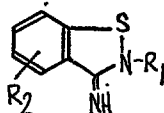
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- N - cyclohexyl - 3 - imino - benzisothiazoline.HCl
Colorless compact prisms of m.p. 166° C.
- N - [4 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl
After recrystallization from ethoxyethanol, colorless crystals of m.p. 160° C.
- 5 N - [3 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl 5
Colorless small needles of m.p. 197° C., from ethanol.
- N - [2 - methyl - cyclohexyl] - 3 - imino - benzisothiazoline.HCl
On recrystallization from DMSO, the compound produces colorless prisms of m.p. 210° C.
- 10 N - benzyl - 3 - imino - benzisothiazoline.HCl 10
This substance was isolated in the form of the free base. The compound forms colorless compact prisms of m.p. 85° C. (from methanol).
- N - phenyl - 3 - imino - benzisothiazoline
This compound was isolated in the form of the free base. Colorless bulbous crystals of m.p. 99°C. (from ethanol).
- 15 N - [4 - methyl - phenyl] - 3 - imino - benzisothiazoline 15
The free base crystallizes from ethanol in the form of long yellowish needles of m.p. 144°C.
- The invention therefore also provides an antimycotic composition comprising a compound according to the invention in admixture with a solid or liquid diluent or carrier. The selection of a particular diluent or carrier and the exact proportions used may of course be in accordance with general practice.
- 20 The invention therefore also provides a method of combating mycotic pests, comprising apply to a mycotic pest habitat a compound according to the invention, alone or in admixture with a solid or liquid diluent or carrier. 25

WHAT WE CLAIM IS:—

1. An N - substituted 3 - imino - benzisothiazoline of the formula:—



in which

- 30 R₁ is an alkyl of 1 to 7 carbon atoms, a cycloalkyl, an aralkyl or an aryl radical, which may be substituted by halogen, nitro, alkyl or alkoxy containing 1 to 6 carbon atoms or dialkylamino containing 2 to 12 carbon atoms, and 30
- R₂ is at least one of hydrogen, halogen, nitro, alkyl and alkoxy containing 1 to 6 carbon atoms and strong acid salts thereof.
- 35 2. N - methyl - 3 - imino - benzisothiazoline.HCl. 35
 3. N - ethyl - 3 - imino - benzisothiazoline .HCl.
 4. N - propyl - 3 - imino - benzisothiazoline .HCl.
 5. N - butyl - 3 - imino - benzisothiazoline.HCl.
 6. N - isobutyl - 3 - imino - benzisothiazoline .HCl.
 - 40 7. N - [β - chloroethyl] - 3 - imino - benzisothiazoline.HCl. 40
 8. N - cyclohexyl - 3 - imino - benzisothiazoline .HCl.
 9. N - [4 - methylcyclohexyl] - 3 - imino - benzisothiazoline.HCl.
 10. N - [3 - methylcyclohexyl] - 3 - imino - benzisothiazoline .HCl.
 11. N - [2 - methylcyclohexyl] - 3 - imino - benzisothiazoline .HCl.
 - 45 12. N - benzyl - 3 - imino - benzisothiazoline .HCl. 45
 13. N - phenyl - 3 - imino - benzisothiazoline.
 14. N - [4 - methyl - phenyl] - 3 - imino - benzisothiazoline.
 15. A process for the preparation of a compound of claim 1 which comprises reacting an N - substituted 3 - halogeno - benzisothiazolium halide with ammonia.
 - 50 16. A process for the preparation of a compound of claim 1 which comprises re- 50



acting an N - substituted 3 - halogeno - benisothiazolium halide with ammonia in methanolic solution at a temperature of 5° to 10°C.

17. A process according to claim 15 or 16 in which the N-substituted 3 - halogeno-benzisothiazolium halide is introduced into an excess of the ammonia.

5 18. A process according to claim 15, substantially as hereinbefore described in the Example. 5

19. The compound of any of claims 1—14 when prepared by the process of any of claims 15—17.

10 20. An antimycotic composition comprising a compound according to any of claims 1—14 and 19 in admixture with a solid or liquid diluent or carrier. 10

21. A method of combating mycotic pests, comprising applying to a mycotic pest habitat (other than the human body) a compound according to any of claims 1—14 and 19, alone or in admixture with a solid or liquid diluent or carrier.

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